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13. ABSTRACT (Maximum 200 Words)

Background: Breast cancer outcomes in black women are worse than in white women. The quality of adjuvant therapy may be poorer in black women. **Purpose**: To investigate the quality of breast cancer adjuvant therapy according to race. **Methods**: Chemotherapy dose proportion, dose intensity, and time between treatment modalities was determined for 489 women treated for non-metastatic breast cancer between 1985 and 2000. Multivariate analyses were used to correct for age and other sociodemographic characteristics, tumor features, and treatment course, such as delays in therapy due to myelosuppression. Archival tumor specimens from 165 subjects were obtained for HER-2 assessment. **Results**: Black race was independently associated with lower dose proportion (.09 lower, $p = .002$) and intensity (.10 lower, $p < .001$) and longer time between treatment modalities. Race and body mass index were independently associated with intentional first cycle dose reductions below standard doses. There was an insufficient number of subjects had HER-2 positive tumors to perform a survival analysis in this subgroup according to quality of chemotherapy. **Conclusions**: The quality of breast cancer adjuvant therapy is poorer in black women. Interventions to improve the quality of care are necessary to eliminate disparities in outcome.

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Introduction

Although the incidence of breast cancer in African-American women is lower than in white women, breast cancer mortality rates and case fatality rates among African-Americans are consistently higher than those among whites (SEER http://www.census.gov). Accounting for extent of disease (localized, regional, distant) does not eliminate and racial disparities in five-year survival rates (SEER http://www.census.gov). There is no evidence that the mortality gap is decreasing, even in a setting where there is equal access to care (Newman et al. 2002). Differences in the quality of chemotherapy received by African-American women may provide an additional explanation for the poorer outcome among African-American women. The benefit of adjuvant chemotherapy on disease-free and overall survival in women with breast cancer is significantly diminished in patients who do not receive full doses of therapy (Bonadonna & Valagussa 1981, Bonadonna et al. 1995). There is ample evidence that many patients who are not treated on a clinical trial do not receive the recommended chemotherapy dose intensity of 85% or more (Link et al. 2001, Lyman et al. 2003, Ottevanger et al. 2002, DeMulder et al. 2002, Schaapveld et al. 2004). This multicenter study focuses on the clinical impact of suboptimal dose/dose intensity in women with HER-2/*neu*-positive tumors, a subgroup in whom optimal chemotherapy may be particularly critical (Muss et al. 1994, Thor et al. 1998). This study involves in-depth review of treatment records of subjects who have received chemotherapy for breast cancer and identification of the HER-2/*neu* oncoprotein on archival tumor specimens. The primary measures of chemotherapy quality (relative dose and dose intensity) will be related to the subjects' clinical outcome. The ultimate goal of the project is to design interventions targeting those factors that lead to lower dose intense chemotherapy in an effort to eliminate disparities in the quality of care of women with breast cancer.

Statement of Work & Research Findings

Women who were treated with adjuvant chemotherapy for stage I, II, or III breast cancer between 1985 and 2000 were included in this study. This is a multicenter study with three sites, Strong Memorial Hospital (Rochester, New York), Henry Ford Health System (Detroit, Michigan), and Singing River Hospital System (Pascagoula, Mississippi).

The progress made for each task in the Statement of Work is described below:

Task 1. Identify eligible subjects by HER-2/*neu* staining on primary tumor samples and begin preparation for data collection, Months 1-12

a) Identify 500 eligible subjects at the four participating sites

b) Process and send samples for staining at central laboratory

c) Stain and interpret HER-2/*neu* staining in black subjects and white controls

d) Design database in preparation for data abstraction

Identification of Subjects (Task 1a)

The original proposal was to conduct this study at four sites; one of our collaborators was not able to participate, leaving the project with three participating sites. Using the respective tumor registry systems at each of the sites, we identified and located charts for a total of 670 subjects. Of these, 579 were eligible (blacks, n = 191; whites, n = 388). Reasons for ineligibility were receipt of primary ("neoadjuvant") chemotherapy (n = 24), chemotherapy interrupted by "sandwich" radiation therapy (n = 20), male breast cancer (n = 2), stage IV disease at diagnosis (n = 3), non-eligible chemotherapy regimen (n = 30), chemotherapy given at another site (n = 5), and previous breast cancer (n = 7). Complete clinical, treatment, and outcomes data were available for 496 (86%) patients. Of these, 164 were black and 332 were white. An equivalent proportion of blacks and whites (86%) had complete data.

Our research progress at the Singing River Hospital System (SRHS) was delayed by two years. Our Principal Investigator, Dr. Raymond Wynn, at that site originally was at Louisiana State University and then took a leadership position at SRHS. There was no infrastructure available to Dr. Wynn when he first arrived. Once he secured a data manager, data abstraction proceeded quite quickly.

Retrieval and Processing of Primary Breast Cancer Tumor Blocks (Tasks 1b and 1c)

Surviving subjects were contacted to obtain written, signed informed consent at the University of Rochester and at the Singing River Hospital System. Twelve subjects at the University of Rochester declined to have their tumor blocks retrieved and assessed for overexpression of the HER-2 oncoprotein. We were unsuccessful at contacting 17 potential subjects. All subjects with available tumor blocks (n = 52) were approached at the Singing River Hospital System. All potential subjects provided written signed informed consent for tumor staining for HER-2. Tumor blocks at the Henry Ford Health System are de-identified, and linking of the clinical information with the HER-2 results was done without identifiers.

Of the 496 subjects with complete clinical data, 208 (42%) had tumor blocks available for HER-2 assessment. Among the black subjects, 65 (40%) had tumor blocks available. Among the white subjects, 143 (43%) had tumor blocks available. This retrieval rate was lower than we had expected, but such a rate is not unusual, particularly as we were retrieving blocks from as long ago as 1985.{5623}{5624} All staining was performed in the Department of Pathology at the University of Rochester by one cytotechnologist and interpreted by the study pathologist.

Satisfactory HER-2 assessment was achieved in 165 cases (80%). Of the tumors of black women, 47 (72%) were successfully assessed for HER-2 overexpression. Of the tumors of white women, 118 (82%) were successfully assessed for HER-2 overexpression. Reasons for lack of success were inadequate sample for assessment and inadequate adherence of sample to the slide.

The procurement and processing of the tumor blocks took much longer than we anticipated. The fourth year of this grant period was requested because of delays in HER-2 assessment. The cytopathologist working on the study had multiple surgeries during the four-year study period, and the pathologist working on the HER-2 interpretation was on medical leave for several months in year 3.

Database Design
(Task 1d)

We have designed and refined a comprehensive database for data entry for subjects in this study using Access 97® (Microsoft Corporation). Data were exported to SAS for analyses.

Task 2. Abstraction of data from records of women whose tumors stain positive for overexpression of HER-2/*neu*, Months 13-24

a) Train data managers in data abstraction

b) Complete data abstraction from records of eligible subjects (approximately 40 subjects at each site = 160 total*)

c) Complete data entry and confirm consistency of data abstraction methods

*Original grant application specified 4 sites with 160 subjects with HER-2 positive tumors. As described in the first paragraph of the Research Progress, we now have three participating sites.

Train Data Managers in Data Abstraction
(Task 2a)

Data managers were trained at each of the sites. The Principal Investigator and the Study Coordinator at the University of Rochester have continuously monitored the quality of data collection and entry. As described above, training of the data manager at the Singing River Hospital System did not begin until Year 3 of the grant period.

Data Abstraction from Records of Eligible Subjects
(Task 2b)

Data collection is complete on all eligible subjects. A total of 579 subjects were eligible. Of these, 496 had complete data. With funding from the Doris Duke Charitable Foundation and additional support, we have been able to complete data abstraction on all subjects who met criteria—including subjects with both HER-2 positive and HER-2 negative tumors. We were also able to perform data abstraction from all of the five hospitals in Rochester, New York under the Doris Duke Charitable Foundation.

Data Entry and Confirm Consistency of the Data Abstraction
(Task 2c)

Data entry is complete. Continuous monitoring of the quality of data by the Principal Investigator and the Study Coordinator at the University of Rochester has ensured consistency of the data.

Task 3. Analysis of data, Months 25-36

a) Design multivariate regression models

b) Conduct analyses

c) Interpret data with investigators in Consortium

d) Begin designing interventions based upon results

Analysis of Data
Tasks 3a, 3b, 3c.

The purpose of this study was to examine patterns of care received for women with primary (non-metastatic) breast cancer. We investigated the quality of chemotherapy as measured by the dose proportion (actual: expected doses of chemotherapy) and the dose intensity (which takes into account the time required to complete chemotherapy). We also examined the time between treatment modalities. **The results of the analyses that follow include the findings of subjects included through the grant reviewed in this report (DAMD 17-00-0422) and through a grant from the Doris Duke Charitable Foundation. The combined funding mechanisms have allowed for analyses in 489 women.** An additional study, described below, demonstrated that insurance status is associated with the likelihood of having one's primary breast cancer stained for HER-2.

Quality of Chemotherapy. The methods and results of these analyses, as well as the interpretation of the data and a discussion of the implications, are described in the enclosed manuscript. In brief, we have demonstrated that black women and overweight and obese women receive lower dose proportion and dose intensity than white women and lean women.(Griggs et al., 2003) In multivariate analyses, dose proportion was .09 lower ($p = .002$), and relative dose proportion was .10 ($p < .001$) lower in non-overweight African-Americans than whites. Obesity was associated with lower dose proportion ($p < .01$) and relative dose proportion ($p < .03$). Race and body mass index were independently associated with intentional first cycle dose reductions below standard dosing regimens. Non-overweight African-Americans ($p < .05$) and overweight and obese African-American and white women ($p < .001$) were more likely to have first cycle dose reductions than non-overweight whites. We have thus demonstrated that black race and obesity are independently associated with suboptimal quality of chemotherapy after controlling for age, coexisting medical problems, and socioeconomic status. We have also shown that first cycle dose reductions (intentional dose reductions) are more common among blacks and heavier women.

Time between Treatment Modalities. We have also examined racial disparities in the duration from diagnosis to surgery, and from surgery to the start of chemotherapy. Data abstracted from medical oncology treatment charts included sociodemographic characteristics (age, race, insurance), comorbid conditions, tumor features (e.g. tumor size, estrogen and progesterone receptor status and nodal involvement), and treatment course (type of surgery, whether the woman had reconstructive surgery, and the timing of diagnosis, definitive surgery, and the

chemotherapy). Women's addresses were mapped to their census-block group to obtain neighborhood estimates of median income.

Subject characteristics were compared by race using t-tests, chi-sq tests and Fisher's exact test as appropriate. The relationship between race and the time between diagnosis and surgery, diagnosis and chemotherapy, and surgery and chemotherapy was examined using Kaplan-Meier curves compared with the log rank test. The independent effect of race was examined in multivariate analyses using Cox's partially nonparametric proportional hazards models. Covariates in these models included age, weight categories, comorbidity shown to delay surgical healing, tumor characteristics, node status, surgery type, year of treatment and treatment site.

Black women experienced significantly longer time periods between diagnosis and the start of chemotherapy (68.1 versus 52.6 days, $p<.001$). Black women also experienced longer durations for both components of this period, from diagnosis to surgery (22.9 versus 13.8 days, $p<.001$) and to a lesser extent, from surgery to the start of chemotherapy (46.9 versus 40.8 days, $p=.04$). The Cox models indicated that black women receiving mastectomy without reconstruction experienced longer durations between diagnosis and chemotherapy than did white women after controlling for the above-described variables.

Women with larger tumors experienced shorter durations from diagnosis to the start of chemotherapy, while women found to have 4 or more positive lymph nodes after surgery progressed more rapidly to their chemotherapy. Insurance status and median per capita income in the census block group were not significantly associated the time to treatment.

The findings from this work were presented at the AcademyHealth annual meeting in 2003. The corresponding manuscript is in preparation. This portion of the project was done in Years 3 and 4

Survival Analysis. The final portion of this project is the survival analysis in women whose tumors overexpressed HER-2. We retrieved tumor blocks from fewer subjects than we had anticipated. We had a 42% tumor block retrieval rate. It is in these patients that dose proportion and relative dose intensity are most important.{Muss, Thor, et al. 1994 3704 /id}{Thor, Berry, et al. 1998 3703 /id} The unexpected number of missing blocks or tumors where the cancer could not be located has decreased the number of potential subjects for the survival analysis substantially. We have HER-2 results on the tumors of 47 black women and 118 white women (total n = 165). Of these 165 tumor blocks, 65 were positive for overexpression of the HER-2 oncoprotein. There was substantial heterogeneity in the regimens that were used in the subjects included in this study. Because of the small number of HER-2 positive tumors and the variety of chemotherapy regimens, we were not able to perform a survival analysis according to HER-2 status and chemotherapy quality as originally proposed in our grant application.

Additional Findings. A supplemental project led by our Investigator at Henry Ford Health System was performed to determine which patient or tumor characteristics were associated with HER-2 ascertainment among breast cancer patients after HER-2 assessment methods were commercially available. Insurance status and expression of the estrogen receptor were shown to be independently associated with HER-2 assessment (Stark et al. 2004). This work was recently published in the *International Journal for Quality in Health Care*. The manuscript is included with this report. This work was done in Years 3 and 4.

Design Interventions to Address Disparities.
(Task 3d.)

Having demonstrated disparities in the quality of breast cancer care according to race, socioeconomic status, and obesity status, we are now designing two additional research projects. The first is a natural outgrowth of the project funded through the Department of Defense. We are submitting a grant application to the National Institutes of Health to expand our network of research sites to include Louisiana State University and George Washington University. We will be collecting clinical and treatment information on 3,000 patients treated for Stage I, II, or III breast cancer. The purpose of the proposed project is to investigate the impact of race, socioeconomic status, and obesity status on the quality of care from diagnosis to completion of all treatment (surgery, chemotherapy, and radiation therapy). We will then examine the impact of the quality of care on breast cancer on breast cancer outcomes. The second project in development is a Patient Navigator Program for patients with abnormal screening mammograms or clinical breast exams. Such programs may help overcome the systematic obstacles faced by vulnerable populations (Freeman & Payne 2000).

Key Research Accomplishments

1. We have developed a network of breast cancer treatment sites.
2. We have developed a data collection system, comprehensive database, and statistical program to calculate dose and dose intensity of a variety of chemotherapy regimens for early-stage breast cancer.
3. We have demonstrated that disparities exist among different ethnic/racial groups in the administration of chemotherapy for early-stage breast cancer.
4. We have demonstrated that the time between various treatment modalities in breast cancer is longer for black women than for whites.
5. We have shown that obesity impacts chemotherapy prescribing patterns.

Reportable Outcomes

1. "Ethnicity and Age Predict Suboptimal Adjuvant Chemotherapy for Breast Cancer," Abstract and Podium Presentation, Annual Meeting of the Academy of Health Services Research, June 2001.
2. "Do Physician Prescribing Patterns Differ by Ethnicity in the Treatment of Localized Breast Cancer?" Abstract, Annual Meeting of the Academy of Health Services Research, June 2001.
3. "Racial Disparity in Breast Cancer Chemotherapy," Presentation at the Henry Ford Health System Cancer Center Grand Rounds, November 30, 2001.
4. "Racial Variation in Breast Cancer Adjuvant Therapy," Cancer Center Grand Rounds, Medical College of Virginia, Richmond, Virginia, February 2002.
5. "Quality of Breast Cancer Adjuvant Chemotherapy in African-American and Caucasian Women," Presented at the San Antonio Breast Cancer Symposium, San Antonio, Texas, December 2002.
6. "Disparities in Breast Cancer Treatment," Presentation, Rochester Clinical Research Curriculum, March 2003.
7. "Racial Disparities in Breast Cancer Care: Evidence for Systematic Disparities in Care" Grand Rounds, Roswell Park Cancer Institute, March 2003.
8. "Racial Disparity in the Dose and Dose Intensity of Breast Cancer Adjuvant Chemotherapy." Manuscript, *Breast Cancer Research and Treatment.* 81:21-31, 2003.
9. Sorbero MES and Griggs JJ. Do African-American Women Experience More Delays in the Treatment of Breast Cancer Than White Women? AcademyHealth Annual Research Meeting, June 2003.
10. Griggs JJ, Sorbero MES, Stark PhD. First Cycle Dose Reductions in African-American and Overweight Women Receiving Breast Cancer Adjuvant Therapy. Presented at American Society of Clinical Oncology Annual Meeting, Chicago, IL June 2003.
11. Stark A, Kucera G, Lu M, Claud S, Griggs J. Influence of health insurance status on inclusion of HER-2/neu testing in the diagnostic workup of breast cancer patients. Manuscript. Internatl J Qual Health Care. 16:1-5.

Conclusions

We have demonstrated that there is systematic disparity in the quality of adjuvant breast cancer chemotherapy according to race, obesity status, and income. Other investigators have demonstrated that the quality of chemotherapy varies in patients treated off of clinical trials (Link et al. 2001, Lyman et al. 2003, Ottevanger et al. 2002, DeMulder et al. 2002, Schaapveld et al. 2004). Our work is the first to examine the impact of race on the quality of chemotherapy and to show that race predicts suboptimal chemotherapy for early stage breast cancer. Biological and socioeconomic differences do not explain the disparity in the treatment. Physician prescribing patterns, manifested by the use of first cycle dose reductions, appear to impart a significant impact on the outcome measures of our study, namely dose proportion and relative dose intensity. Women who are obese, black, and living below the median income are most likely to receive intentionally reduced chemotherapy doses. The systematic difference in the quality of chemotherapy may contribute to the higher case-fatality rate among African-American women and economically disadvantaged women with breast cancer.

We have also shown that the time to proceed through the multiple types of treatment, that is, surgery, chemotherapy, and radiation therapy, is longer in black women. A recent article demonstrated that time to treatment is longer in blacks but did not examine each of the intervals as we have (Gwyn et al. 2004).

Thus far, our measures are process measures of quality of care. If such dose reductions have an impact on outcome, and they appear to,(Morrow et al. 2002, Budman et al. 1998) we may have identified a contributing factor to the inferior breast cancer outcomes seen in black women, heavy women, and poorer women. Interventions to eliminate the disparities in the quality of chemotherapy have the potential to improve the quality of care for minority women and economically disadvantaged women with breast cancer. Management of localized breast cancer is complicated and requires coordination of care across multiple specialties. Our work raises the possibility that the process of care differs between racial/ethnic and socioeconomic groups. Our ongoing research program will be linking processes of care with outcomes. We will be submitting an R01 to the National Institutes of Health for February 1, 2005. This grant application will also be testing interventions to eliminate disparities in the quality of chemotherapy.

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Appendix

List of Personnel:

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Principal Investigator	Jennifer J. Griggs, MD, MPH
Pathologist	Linda M. Schiffauer, MD
Sr. Project Coordinator	Susanne Heininger, RN

Henry Ford Health System

Site Investigator	Azadeh Stark, PhD
Site Project Coordinator	Gena Kucera, MPH
Histotechnologist	Bridget Elington

Singing River Health System

Site Investigator	Raymond B. Wynn, MD
Data Manager	Carolyn Freeman

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Report

Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy

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Key words: breast cancer, chemotherapy, obesity, racial disparity

Summary

Purpose. The purpose of this study was to investigate the impact of race and obesity on dose and dose intensity of adjuvant chemotherapy.

Methods. We abstracted data on patient/tumor characteristics, treatment course, physicians' intention to give a first cycle dose reduction, and reasons for dose reductions/delays from oncology records of 489 women treated from 1985 to 1997 in 10 treatment sites in two geographical regions. Administered doses and dose intensity were compared to standard regimens. Multivariate regression models determined the impact of race and body mass index (BMI) on dose proportion (actual:expected doses) and relative dose intensity (RDI) controlling for patient characteristics, comorbidity, chemotherapy regimen, site, and year of treatment. Logistic regressions explored race and BMI versus use of first cycle dose reductions.

Results. African-Americans received lower chemotherapy dose proportion and RDI than whites (0.80 vs. 0.85, $p = 0.03$ and 0.76 vs. 0.80, $p = 0.01$). In multivariate analyses, dose proportion was 0.09 lower ($p = 0.002$), and RDI was 0.10 ($p < 0.001$) lower in non-overweight African-Americans than whites. Obesity was associated with lower dose proportion ($p < 0.01$) and RDI ($p < 0.03$). Race and BMI were independently associated with first cycle dose reductions. Non-overweight African-Americans ($p < 0.05$) and overweight and obese African-American and white women ($p < 0.001$) were more likely to have first cycle dose reductions than non-overweight whites.

Conclusion. We identified systematic differences in the administration of chemotherapy given to African-Americans and to overweight and obese women. These differences may contribute to documented disparities in outcome.

Introduction

The incidence of breast cancer is lower in African-American women, but breast cancer mortality rates and case fatality rates among African-Americans are consistently higher than among whites [1]. The incidence of breast cancer in 1999, for example, was 123.9 per 100,000 in black women versus 143 per 100,000 in white women, but corresponding mortality rates were 35.8 per 100,000 in blacks versus 26.3 per 100,000 in whites [1]. Even after correction for stage at presentation and tumor biology, disparities in outcome persist [2–4]. Adjustment for socioeconomic status (SES) accounts for some but generally not all of the association between race and poorer outcome [2, 3, 5–10].

African-Americans treated on chemotherapy protocols appear to benefit from adjuvant chemotherapy with not only the same relative risk reduction in breast cancer mortality but also similar stage-specific outcome [11, 12]. This finding supports the conjecture that uniform treatment results in uniform outcome and argues against the hypothesis that race confers an independent deleterious effect on disease-specific outcome.

Large retrospective analyses suggest that the beneficial impact of adjuvant chemotherapy on disease-free and overall survival in women with breast cancer is diminished when full doses of therapy are not given [13–17]. Studies addressing the use or planned use of adjuvant therapy in African-Americans and whites have generally not demonstrated disparities in the use or intention to use chemotherapy [3, 18].

We hypothesized that, among women who do receive chemotherapy, there are systematic differences in the administration of chemotherapy given to African-American and white women. The possibility that differences exist in the delivery of chemotherapy has been raised [2, 19] but not well studied. We also investigated the impact of obesity on prescribing patterns for African-American and white women undergoing adjuvant breast cancer chemotherapy. The practice of dose reduction in overweight and obese women continues [20] despite evidence that using actual body weight for chemotherapy dose calculations is safe [21, 22]. As obesity is more prevalent in African-Americans [23, 24], the practice of basing doses on ideal or adjusted body weight might lead to systematically lower doses in African-Americans.

Subjects and methods

Study subjects. We identified African-American and white women as potentially eligible using the Monroe County (New York) and Henry Ford Health System (Michigan) tumor registries. Subjects identified were treated at 10 treatment sites, including university and community hospitals (five of six treatment sites in Rochester, New York and all five medical oncology treatment sites within the Henry Ford Health System in Detroit, Michigan). Eligibility criteria included treatment between 1985 and 1997 with cyclophosphamide-containing adjuvant chemotherapy for localized or regional (stages I, II, or III) breast cancer. Patients treated with primary (neoadjuvant) chemotherapy, chemotherapy interrupted by radiation ('sandwich radiation'), or on high-dose chemotherapy protocols were excluded. We also excluded women who had had a previous breast cancer.

Data collection. The University of Rochester Research Subjects Review Board (RSRB #08217) and the Henry Ford Health System Institutional Review Board (HFHS IRB #900) approved the data collection protocol. Six trained abstractors performed the chart audits. A senior health project nurse at the University of Rochester repeated the data abstraction on at least 30 charts reviewed by each of the six abstractors and on a random sample of 125 subjects included in the final database. The senior project nurse did all of the data entry.

We abstracted detailed information from the medical oncology charts and treatment records on (1) subject characteristics, including age, self-assigned race/ethnicity, insurance type, address for census block group assignment, height, weight, and coexisting medical conditions (see below), (2) tumor characteristics, including tumor size, number of lymph nodes involved, estrogen receptor (ER) and progesterone receptor (PR) status, and histologic grade, (3) chemotherapy regimen and treatment course, dates of treatment, dose of each drug administered, body surface area used for calculation of the drug doses, and whether a dose reduction from standard doses was used for the initial cycle of chemotherapy, (4) treatment site, (5) reasons for changes in chemotherapy doses or delays in treatment, side effects, hospitalizations, and discontinuation of therapy. White blood cell counts and absolute neutrophil counts (ANC) were recorded whenever available. Coexisting illnesses were recorded using the conditions in the Charlson index [25]. Menopausal status was determined using the medical oncologists' notes in the medical oncology record, which generally contained enough information to make a determination.

For patients treated in Rochester, the medical record was used to identify whether or not patients had private insurance. For the Henry Ford Health System patients, information on insurance was collected from the Patient Master Index database, a central repository for data on patient encounters at Henry Ford Hospital and all HFHS satellites. Those with Medicare were identified as having private insurance if they indicated having a supplemental policy in addition to Medicare Part A.

For each subject, the address at the time of diagnosis was used to identify the census block group. The socioeconomic information for the census block group, including measures of income and education, was determined from 1990 census data using Landview®III Environmental Mapping Software (US Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1997). The use of census block group assignment in the assessment of missing individual level SES data has been shown to generate data that correlates with individual level data [26].

The *actual* doses of chemotherapy subjects received were summed across all visits to determine the total dose of each drug. The *expected* doses of chemotherapy were determined using height, weight at the time of the first treatment, and calculated body surface area according to standard chemotherapy protocols. The actual and expected durations of chemotherapy were also determined for each subject.

Outcome measures. We measured four characteristics of chemotherapy treatment. Each measure was calculated for each subject.

(1) Dose proportion: ratio of actual to expected doses of chemotherapy in standard adjuvant chemotherapy regimens. This was calculated for each drug in the chemotherapy regimen. The ratios were then averaged to determine an overall dose proportion for the regimen.
(2) Time ratio: ratio of the actual to expected duration of chemotherapy.
(3) Relative dose intensity (RDI): dose proportion $\times$ 1/time ratio.
(4) Reductions of doses at the initiation of treatment: a measure of whether or not a reduction in the doses of chemotherapy drugs used at the initiation of treatment was documented in the treating provider's note in the subject's chart.

Statistical analyses. Descriptive analyses of the subject characteristics and the outcome measures were performed for the entire sample and by racial/ethnic group. Comparisons between groups were performed using Student's *t*-tests, chi-squared tests, and Fisher's exact tests as appropriate. All tests for significance were two-sided. Dose proportion, the time component, and RDI were analyzed using multivariate regression to determine the effect of race controlling for other subject characteristics, including the body mass index (BMI) categories of the National Heart, Lung, and Blood Institute [27] and initial white blood cell count, tumor characteristics, chemotherapy regimen, treatment site, year of treatment, and reasons for dose changes or treatment delays as independent variables. We included a full set of year of diagnosis indicator variables to account for time effects. We tested down to a specification that included a single indicator variable to identify if treatment occurred after 1993. The multivariate analyses for dose proportion and RDI were performed with cyclophosphamide alone as well as for the other drug(s) in the regimen without the cyclophosphamide. This was done in an attempt to reduce the variability that would arise from rounding doses of oral cyclophosphamide.

Due to the degree of multicollinearity on the SES variables, the dichotomous variable for per capita income above the sample median was the only census block group level SES measure kept in the models. The results were robust to a variety of specifications for the SES variables. Interactions between race and the other covariates were also examined.

As the outcome measures were sufficiently skewed as to result in heteroskedastic error terms, we explored simple transformations for the measures that would normalize the error terms, such as the natural log of the measure. Complex transformations, which would reduce the interpretability of our results, would be required to normalize the error terms. Hence, we opted to use robust standard errors to account for the heteroskedasticity in the error term rather than transform the dependent variables [28]. This generates unbiased parameter estimates but is a less efficient analytical method, resulting in wider confidence intervals than transforming the dependent variables.

Dose reductions at the initiation of treatment were modeled using logistic regression controlling for subject characteristics, including race, age, BMI categories, and initial white blood cell count, tumor characteristics, chemotherapy regimen, treatment site, and year of treatment, parameterized as described above.

Analyses were performed using SAS Version 8.01 (SAS Institute, Inc., Cary, NC) and Stata 7.0 (Stata Corporation, College Station, TX).

Results

Subject characteristics. The African-Americans included in our study were similar to the whites with respect to age, menopausal status, tumor size and number of positive nodes (Tables 1 and 2). African-Americans, however, were more likely to be obese (BMI $\geq$ 30, 43% vs. 21%, $p < 0.0001$) and to live in census block groups with lower per capita income ($12,304 vs. $17,700, $p < 0.0001$). African-Americans were less likely to be privately insured (84% vs. 94%, $p < 0.01$) and were less likely to have ER positive tumors (46% vs. 66%, $p < 0.001$). In addition, African-American women were more likely than white women to have coexisting illnesses. For example, 19% of the African-Americans in our sample had a Charlson index of 1 compared to 8% of the

Table 1. Subject characteristics by race, $n = 489$

	Whites $n = 380$	African-Americans $n = 109$	p-value
Mean age (SD)	48.5 (10.2)	48.6 (10.9)	NS
Menopausal status, n (%)			
Premenopausal	217 (58)	54 (50)	NS
Perimenopausal	25 (7)	8 (7)	
Postmenopausal	134 (36)	46 (43)	
Unknown	4 (0.01)	1 (1)	
Charlson index, n (%)			
0	337 (89)	85 (78)	0.02
1	32 (8)	21 (19)	
2	8 (2)	2 (2)	
3+	3 (1)	1 (1)	
BMI categories, Ref. [27]			
Mean (SD)	26.8 (5.9)	29.5 (7.0)	<0.001
Underweight (BMI $\leq$ 18.5), n (%)	9 (2.3)	3 (2.8)	
Healthy weight (18.5 < BMI < 25), n (%)	156 (41)	29 (26)	
Overweight (25 $\leq$ BMI < 30), n (%)	134 (36)	31 (29)	
Obese (BMI $\geq$ 30), n (%)	81 (21)	46 (43)	
Mean first WBC (SD)	7.1 (2.0)	6.3 (1.9)	<0.001
Use of granulocyte colony stimulating factor, n (%)	22 (5.8)	6 (5.5)	NS
Census block group below poverty level, n (%)	27 (7)	24 (22)	<0.001
Per capita income (SD)	17700 (7000)	12300 (5900)	<0.001
Average median income (SD)	41870 (16789)	26519 (14600)	<0.001
Private insurance, n (%)	357 (94)	92 (84)	0.01
Underinsured, n (%)	24 (6)	17 (16)	<0.001
Dose proportion (mean)	0.85	0.80	0.03
Dose intensity (mean)	0.80	0.76	0.01

whites ($p = 0.001$). There were no differences in the proportion of subjects with higher Charlson scores (2 or more).

Dose proportion and RDI. The mean unadjusted dose proportion among African-Americans was 0.80 compared with a mean unadjusted dose proportion of 0.85 among the whites (difference in dose proportion of 0.05, $p = 0.03$). The mean unadjusted RDI was likewise lower for African-Americans than for whites (0.76 vs. 0.80, $p = 0.01$). There was no difference in the time component between the two groups (1.07 for African-Americans and 1.06 for whites, $p = 0.87$). Seventy-two percent of the whites received a dose proportion of 0.80 or greater compared with only 61% of the African-Americans ($p = 0.02$).

Multivariate regression results. We performed multivariate analyses controlling for tumor characteristics, coexisting medical problems, obesity, per capita income of the subjects' census block group, insurance type (private v.s. non-private), chemotherapy regimen, treatment site, whether chemotherapy was given before or after 1993, and reasons for dose changes and treatment delays (Table 3). The reasons for dose changes and delays are listed in Table 4. Fifteen subjects had missing data, such as tumor size and lymph node status, and were excluded from the multivariate analyses.

Dose proportion. The dose proportion in non-overweight African-Americans was 0.09 lower than in non-overweight whites ($p = 0.002$). Similarly,

Table 2. Tumor characteristics by race, $n = 489$

	Whites ($n = 380$)	African-Americans ($n = 109$)	p-value
Tumor size, n (%)			
<2 cm	173 (46)	39 (36)	0.05
2–5 cm	177 (47)	54 (50)	
>5 cm	30 (8)	16 (15)	
Lymph node involvement, n (%)			
None	136 (36)	41 (38)	0.12
1–3	147 (39)	52 (48)	
4–9	54 (14)	8 (7)	
10+	40 (10)	8 (7)	
Estrogen receptor, n (%)			
Positive	252 (66)	50 (46)	0.001
Negative	122 (32)	58 (53)	
Unknown	6 (2)	1 (1)	
Progesterone receptor, n (%)			
Positive	228 (60)	50 (46)	0.05
Negative	139 (37)	56 (51)	
Unknown	13 (3)	3 (3)	

overweight and obese women, regardless of race, received substantially lower dose proportions than did non-overweight whites (−0.11 in overweight African-Americans, $p < 0.001$; −0.08 in obese African-Americans, $p < 0.01$; −0.02 in overweight whites, $p = 0.14$; −0.09 in obese whites, $p < 0.001$). Initial (pre-treatment) white blood cell count was related to dose proportion in that each rise of $1000\,\mu l^{-1}$ in the white blood cell count was associated with an increase in dose proportion of 0.007. Women with the largest tumors (over 5 cm) received higher dose proportion, which was marginally significant. There were also significant variations in dose proportion by chemotherapy regimen (Table 3). Women treated before 1993 received significantly lower dose proportion. Dose changes due to low ANC, delays or termination of treatment due to side effects, and patients' deciding to terminate chemotherapy were significantly associated with lower dose proportion. Other tumor characteristics, coexisting medical problems, age at diagnosis, insurance status, per capita income and changing regimens were not associated with dose proportion. There were no significant changes in the findings when the dose proportion of cyclophosphamide alone was the dependent variable or when cyclophosphamide was excluded from the analyses.

Time ratio (Table 3). The ratio of the actual to expected time to completion of chemotherapy did not differ between African-Americans and non-overweight whites. The time ratio was, however, 0.04 *lower* in overweight and obese whites than in non-overweight whites. Initial white blood cell count was negatively associated with the time ratio. Changing chemotherapy regimens was associated with a higher time ratio, indicating that changing regimens increased the amount of time it takes women to complete their chemotherapy. In addition, delays in treatment due to low ANC, low white blood cell counts, and missed appointments lengthened the time it took women to complete chemotherapy. There were also significant variations in the time ratio by site and chemotherapy regimen. Age at diagnosis, coexisting medical problems, tumor characteristics, insurance status and per capita income were not significantly related to the time ratio.

Relative dose intensity (Table 3). The RDI in non-overweight African-Americans was 0.10 lower than in non-overweight whites ($p < 0.001$). Overweight and obese African-Americans and obese whites also had significantly lower RDI than non-overweight whites (−0.10 for overweight African-Americans, $p < 0.01$; −0.07 for obese African-Americans, $p < 0.03$, and −0.06 for obese whites, $p < 0.01$). Initial (pre-treatment) white blood cell count was associated with an increase in RDI of 0.012 for each $1000\,\mu l^{-1}$ increase in white blood cell count. Dose changes due to low ANC, delays in treatment due to low white blood cell counts, delays due to missed appointments, and delays or termination of treatment due to side effects were significantly associated with lower RDI, as were patients' deciding to terminate chemotherapy. There were also significant variations by chemotherapy regimen. Increasing age at diagnosis was associated with small but statistically significant decreases in RDI. Women with private insurance received lower RDI. Changing regimens and being treated before 1993 were associated with lower RDI. Women with the largest tumors, those over 5 cm, received higher RDI. Other tumor characteristics, coexisting medical problems, and per capita income were not associated with RDI. There were no significant changes in the findings when the RDI of cyclophosphamide alone was the dependent variable or when cyclophosphamide was excluded from the analyses.

Table 3. Multivariate regression on dose proportion, time ratio and dose intensity, selected results

Variable	Dose proportion		Time ratio		RDI	
	Coefficient (SE)	*p*	Coefficient (SE)	*p*	Coefficient (SE)	*p*
Healthy weight and underweight African-American	−0.089 (0.029)	**0.002**	0.010 (0.016)	0.52	−0.101 (0.030)	**0.001**
Overweight African-American	−0.113 (0.032)	**0.001**	−0.027 (0.021)	0.21	−0.098 (0.032)	**0.003**
Obese African-American	−0.076 (0.029)	**0.009**	−0.025 (0.021)	0.23	−0.066 (0.026)	**0.012**
Overweight white	−0.024 (0.016)	0.14	−0.037 (0.013)	**0.006**	0.003 (0.017)	0.86
Obese white	−0.085 (0.022)	**<0.001**	−0.036 (0.015)	**0.02**	−0.058 (0.022)	**0.009**
Age at diagnosis	−0.001 (0.0007)	0.12	0.0002 (0.0006)	0.74	−0.002 (0.0007)	**0.03**
Comorbid conditions (Charlson index ≥ 1)	0.021 (0.020)	0.29	−0.002 (0.017)	0.89	0.026 (0.021)	0.21
No lymph node involvement	−0.026 (0.016)	0.11	−0.012 (0.013)	0.33	−0.022 (0.016)	0.18
Private insurance	−0.040 (0.027)	0.14	0.008 (0.021)	0.71	−0.053 (0.027)	**0.05**
Census block group per capita income > median	0.011 (0.015)	0.48	0.010 (0.012)	0.41	0.003 (0.016)	0.85
Dose changes due to low ANC	−0.035 (0.014)	**0.01**	–	–	−0.026 (0.012)	**0.03**
Delays due to low ANC	0.023 (0.008)	**0.004**	0.027 (0.007)	**<0.001**	−0.001 (0.007)	0.87
Delays due to low white blood cell counts	−0.001 (0.008)	0.90	0.028 (0.007)	**<0.001**	−0.018 (0.008)	**0.02**
Delays due to missed appointments	−0.008 (0.026)	0.76	0.056 (0.018)	**0.002**	−0.048 (0.024)	**0.04**
Delays and termination of treatment due to side effects	−0.167 (0.036)	**<0.001**	0.008 (0.019)	0.69	−0.172 (0.032)	**<0.001**
Termination of treatment due to patient decision	−0.241 (0.084)	**0.004**	−0.111 (0.046)	**0.02**	−0.169 (0.084)	**0.04**
Treated before 1993	−0.042 (0.016)	**0.008**	−0.017 (0.013)	0.17	−0.035 (0.156)	**0.03**
Compared to CA*						
CAF intravenous, day 1, q. 21 days	−0.173 (0.029)	**<0.001**	0.028 (0.027)	0.30	−0.183 (0.030)	**<0.001**
CAF oral, days 1, 8, q. 28 days	−0.101 (0.027)	**<0.001**	−0.075 (0.020)	**<0.001**	−0.057 (0.029)	**0.05**
CMF intravenous, days 1, 8, q. 21 days	−0.052 (0.020)	**0.008**	0.048 (0.019)	**0.01**	−0.084 (0.023)	**<0.001**
CMF intravenous, day 1, q. 21 days	−0.036 (0.034)	0.29	0.050 (0.033)	0.13	−0.071 (0.035)	**0.04**
CMF intravenous, days 1, 8, q. 28 days	−0.001 (0.047)	0.98	−0.102 (0.050)	**0.04**	0.090 (0.059)	0.13
CMF oral, days 1, 8, q. 28 days	−0.087 (0.019)	**<0.001**	−0.047 (0.019)	**0.012**	−0.057 (0.022)	**0.01**
CNF	−0.088 (0.034)	**0.010**	−0.052 (0.031)	0.09	−0.116 (0.036)	**0.001**
Change in regimen	−0.029 (0.029)	0.31	0.127 (0.019)	**<0.001**	−0.057 (0.024)	**0.02**

* C = cyclophosphamide, A = doxorubicin (adriamycin), M = methotrexate, F = 5-fluorouracil, N = mitoxantrone.

First cycle dose reductions. Logistic regressions on dose reductions at the initiation of treatment generated findings similar to the patterns described above (Table 5). Non-overweight African-Americans (OR = 3.7, $p < 0.05$), overweight African-Americans (OR = 19.4, $p < 0.001$), obese African-Americans (OR = 11.5, $p < 0.001$), overweight whites (OR = 5.2, $p < 0.001$), and obese whites (OR = 21.4, $p < 0.001$) were more likely to have first cycle dose reductions than were non-overweight whites. Initial dose reductions were more common before 1993 (OR = 3.5, $p < 0.001$). Women living in census block groups with per capita incomes above the median for our sample were less likely to have their first cycle doses reduced. There were significant differences by treatment site in the tendency to reduce doses at the start of treatment. Tumor characteristics, chemotherapy regimen, co-existing medical problems, age at diagnosis, white blood cell count at the start of treatment, and insurance status were not associated with initial cycle dose reductions.

Table 4. Frequency of dose changes and delays in treatment by race

Variable	Whites	African-Americans	*p*-value
Dose changes and number of dose changes, *n* (%)			
Dose changes due to low ANC, *n* (%)	75 (19.7)	17 (15.6)	NS
Mean number for those having dose changes	1.4	2.2	NS
Dose changes due to low white blood cell counts, *n* (%)	64 (16.8)	18 (16.5)	NS
Mean number for those having dose changes	1.5	1.8	NS
Dose changes due to side effects, *n* (%)	56 (14.7)	12 (11.0)	NS
Mean number for those having dose changes	1.3	1.2	NS
Dose changes due to weight loss, *n* (%)	10 (2.6)	5 (4.6)	NS
Mean number for those having dose changes	1.5	1.0	NS
Delays and number of delays			
Delays due to acute illness, *n* (%)	17 (4.7)	12 (11.0)	**0.01**
Mean number for those having delays	1.0	1.3	0.10
Delays due to hospitalization, *n* (%)	26 (6.8)	1 (0.9)	**0.02**
Mean number for those having delays	1.2	1.0	NS
Delays due to low ANC, *n* (%)	155 (40.8)	27 (24.8)	**0.002**
Mean number for those having delays	1.6	2.0	NS
Delays due to low white blood cell counts, *n* (%)	114 (30.0)	28 (25.7)	NS
Mean number for those having delays	1.7	2.0	NS
Delays due to missed appointments, *n* (%)	3.2 (12)	8.3 (9)	**0.02**
Mean number for those having delays	1.1	1.8	0.07
Delays and termination of treatment due to side effects, *n* (%)	30 (7.9)	7 (6.4)	NS
Mean number for those having delays	1.1	1.1	NS
Delays due to surgical complications, *n* (%)	2 (0.5)	2 (1.8)	NS
Mean number for those having delays	1	1.5	NS
Delays due to vacations, *n* (%)	11 (2.9)	2 (1.8)	NS
Mean number for those having delays	1.1	1.0	NS
Termination of treatment due to patient decision, *n* (%)	4 (1.1)	4 (3.7)	0.06

Table 5. Logistic regression to predict dose reductions at initiation of treatment, selected results

Variable	Odds ratio	95% CI	*p*
Healthy weight and underweight white	1.00	–	–
Healthy weight and underweight African-American	3.73	1.27–10.96	**0.02**
Overweight African-American	19.39	4.57–82.21	**<0.001**
Obese African American	11.54	3.21–41.54	**<0.001**
Overweight white	5.19	2.19–12.29	**<0.001**
Obese white	21.40	7.88–58.10	**<0.001**
Age at diagnosis	1.02	0.99–1.05	0.18
Presence of comorbidity	0.50	0.18–1.36	0.17
White blood cell count at start of chemotherapy	1.02	0.86–1.21	0.81
Private insurance	1.55	0.56–4.28	0.40
Census block group per capita income > median	0.49	0.25–0.98	**0.04**
Treated before 1993	3.48	1.63–7.41	**0.001**

Discussion

We have identified systematic differences in the administration of chemotherapy given to African-American women and to overweight and obese women regardless of race. African-Americans and overweight and obese women in our sample received lower adjuvant chemotherapy dose proportion and dose intensity after correcting for clinical and other sociodemographic characteristics. We have also demonstrated that more African-Americans had chemotherapy dose reductions for the first cycle of treatment, independent of weight and that overweight and obese women had more initial dose reductions, independent of race. The relationships between race and BMI and our outcome measures of dose proportion, dose intensity, and first cycle dose reductions were strengthened when we controlled for tumor characteristics, coexisting medical problems, income, type of insurance, and reasons for dose changes and treatment delays (including missed appointments).

Biological and medical reasons, such as differences in tolerance of therapy, comorbidity, or leukocyte counts, do not explain the differences in adjuvant chemotherapy treatment between African-American and white women. There is no evidence in our subjects that the African-American patients experienced more chemotherapy dose delays due to side effects than whites, and in fact others have found that there may be greater tolerance of therapy among African-Americans [29]. We also found no evidence that delays due to low ANC account for the lower dose proportion and RDI among African-Americans; more of the whites in our sample had delays in treatment due to low ANC (40.8% of whites v.s. 24.8% of African-Americans, $p = 0.002$). Thus, despite the association of black race with lower leukocyte counts [30, 31], we found no evidence that lower white blood cell counts accounted for the difference in dose proportion or RDI among the whites and African-Americans in our sample.

Measures of SES, such as per capita income of the census block group and the type of health care insurance, do not appear to play a role in the treatment differences we found. It is likely that SES would play a greater role in patterns of care such as referral for chemotherapy, recommendations for chemotherapy, and perhaps acceptance of therapy by the patient rather than the quality of chemotherapy administered once the decision to treat with adjuvant chemotherapy is made. Missed appointments, more common in the African-Americans, were associated with a lower dose intensity and may reflect the challenges posed by economic obstacles, such as difficulties with transportation or with job-related barriers. A limitation of this study is the fact that income and education information were not available at the level of the individual. Most of our measures of SES (other than type of insurance) are based on census block group assignment. The use of census-level data has been validated as a method for overcoming missing socioeconomic data in patient records [26], but had we been able to collect individual-level SES information, such as income, education, wealth, and occupation, we may have found an association with SES and our measures of quality of care. Moreover, chart audit, no matter how detailed, cannot provide information on family roles, such as care of young children or elderly parents, and social support networks. These factors may account for some of the observed treatment differences between ethnic groups.

Much of the literature on health care disparities has demonstrated that African-Americans are less likely than whites to receive intervention for the same condition. For example, Bach et al. demonstrated that African-Americans are less likely to have potentially curative surgery for stage I or II lung cancer [32], and Mandelblatt et al. recently confirmed previous findings that African-American Medicare beneficiaries are less likely to have radiation therapy after breast conserving surgery [33]. In these cases, it is difficult to determine at which point in the process of care the disparity arises: Are patients not being referred for surgery or radiation? Are they not being offered such therapies? Or are they declining treatments that are offered to them? Our study focuses on the patterns of care in patients who have been referred to medical oncology care, have been advised to receive chemotherapy, and have agreed to start adjuvant chemotherapy. Our process measures of dose proportion and RDI are focused therefore on what has been called 'realized access', that is, access to and receipt of high quality care necessary for favorable outcomes [34]. It appears that African-American women are experiencing a different process of care than the white women and that two of the possible factors – biological and socioeconomic factors – do not explain these variations.

An additional explanation for the racial disparities in the administration of chemotherapy we describe is that interactions between health care providers and their African-American patients differ from those with

their white patients [35–38]. Health care providers, the majority of whom are non-minority, may hold beliefs and assumptions, conscious or unconscious, about their patients' ability to comply with or to tolerate chemotherapy and the side effects, and these assumptions may differ according to patient race/ethnicity. In a survey of 193 physicians with a total of over 618 patient encounters, physicians perceived African-American patients as, among other things, less likely to adhere to medical advice, more likely to lack social support, and less likely to participate in cardiac rehabilitation [37]. In our study, the association between race and first cycle dose reductions may reflect similar differences in physician assumptions about their African-American patients in terms of the patients' social support or ability to tolerate chemotherapy. The disparities in care that we have described may also reflect communication gaps between patient and provider about, for example, the goals of therapy, the anticipated side effects, the management of side effects, and the potential impact of dose reductions and delays [35, 37, 39].

As with African-American women, overweight and obese women appear to be experiencing systematic differences in chemotherapy administration independent of comorbidity, SES, treatment site, and age. Multiple investigators have challenged the practice of reducing chemotherapy doses in obese women, a practice motivated by a desire to avoid excessive toxicity. There is mounting evidence that obese women do not experience increased toxicity when dosed according to actual body weight and that the use of ideal or adjusted body weight may in fact compromise efficacy [21, 22, 40, 41].

Of note, our findings did not apply only to the obese women (BMI ≥ 30). Compared to healthy weight and underweight whites, whites who are classified as 'overweight' ($25 \leq$ BMI < 30) were over five times as likely to have a first cycle dose reduction, and overweight African-Americans were 19 times more likely to experience such a dose reduction. Our results are similar to those in a study of over 500 women treated with breast cancer adjuvant chemotherapy between 1990 and 1998 at a single site in Toronto, Ontario. In this study, the majority of patients prescribed a first cycle dose reduction were overweight rather than obese [20]. Our finding that dose reductions for the first cycle of chemotherapy were less common after the 1993 suggests that some providers have changed their prescribing practices for some of their patients.

We studied women treated before the widespread use of granulocyte colony stimulating factor (G-CSF) in patients undergoing breast cancer adjuvant chemotherapy. Practice patterns and the resulting dose proportion and dose intensity may be altered by use of G-CSF; the impact of G-CSF on dose proportion and dose intensity in different populations would be an area worth investigating.

Further exploration of the underlying reasons for these discrepancies in the administration of adjuvant chemotherapy may identify correctable causes of outcome disparity in breast cancer. Dose proportion and dose intensity of standard dose adjuvant chemotherapy, measured using the RDI or the summation dose intensity of Hryniuk et al.[42], may represent measures of quality of care [43] that could be used further in examining disparities in cancer outcome. In particular, the practice of first cycle dose reduction that we observed suggests differences in prescribing patterns according to patient characteristics.

Would our findings be replicated in other populations in, for example, other geographic locations and other practices? If so, the strength of the associations between race and BMI with dose proportion and intensity would be compelling. If our findings were not consistently seen in other settings, such variability in practice would further suggest that dose proportion, dose intensity, and the use of first cycle dose reductions are all modifiable patterns of care.

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Influence of health insurance status on inclusion of HER-2/*neu* testing in the diagnostic workup of breast cancer patients

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Abstract

Objectives. To assess the prevalence of HER-2/*neu* testing in a community-based health care system shortly after the approval of several laboratory kits for HER-2/*neu* testing for diagnostic purposes by the US Food and Drug Administration and to discern the best discriminating variables for inclusion of the test in the diagnostic workup of breast cancer patients.

Design. A retrospective cross-sectional study was designed to analyze data for the period beginning 1 January 1999 and ending 31 December 2000.

Setting. Henry Ford Health System, the largest health care system in southeastern Michigan, is a comprehensive, self-contained system.

Study participants. Four hundred and fifty-one women diagnosed with primary invasive breast cancers were consecutively sampled from the tumor registry of the Henry Ford Health System.

Results. The proportion of women tested for HER-2/*neu* increased by 2-fold during year 2 of the observation. Absence of estrogen receptors (OR = 1.96, 95% CI 1.15–3.21), physicians with specialty in surgery (OR = 6.21, 95% CI 2.88–13.33, $P = 0.0001$), and having a capitated insurance (OR = 1.59, 95% CI 1.06–2.44, $P = 0.027$) were associated with HER-2/*neu* testing.

Conclusion. Absence of estrogen receptors was the only pathological characteristic associated with HER-2/*neu* testing. The effect of specialization in surgery on the increased likelihood of HER-2/*neu* testing can be explained mostly by the 'patient volume effect'. The observed disparity in the delivery of innovative diagnostic approaches to cancer patients was influenced by the type of health insurance. Implementation of institutional policies can improve in providing universal quality of care for all patients regardless of their health insurance.

Keywords: biomarker, breast cancer, health insurance, HER-2/*neu*

Introduction

Recent advances in biotechnology have made the concept of the formulation of molecular targeted adjuvant therapy a reality [1]. The human epidermal growth factor receptor-2 (HER-2/*neu*) is a well-characterized biomarker in the biology of breast cancer which has had immediate impact on clinical medicine. The HER-2/*neu* biomarker is an independent prognostic marker and is associated with a relative resistance to anthracycline-based chemotherapy and possibly tamoxifen therapy [2–6]. HER-2/*neu* testing among women diagnosed with stage IV breast cancer identifies potential candidates for Herceptin adjuvant antibody treatment [6].

In 1998, the US Food and Drug Administration approved several laboratory kits for evaluation of the HER-2/*neu* biomarker in clinical settings [7–9]. Two years later, the College of American Pathologists and the American Society of Clinical Oncology issued a series of recommendations regarding the significance of HER-2/*neu* testing in the diagnostic workup of breast cancer patients [10,11]. Despite extensive data indicating the value of HER-2/*neu* testing in clinical settings, the availability of approved laboratory kits, and recommendations from the two organizations, it was not until 2001 that several large health care facilities took initiatives to implement institutional policies to incorporate testing for the HER-2/*neu* biomarker in the diagnostic workup of breast cancer patients.

To our knowledge, no systematic investigation has been conducted to assess the variables that discriminate the inclusion of a novel biomarker with diagnostic value in the clinical workup of cancer patients. We undertook a retrospective

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cross-sectional study to evaluate the proportion of women who were tested for HER-2/*neu* and to determine the variables that were associated with HER-2/*neu* testing of a woman at the initial clinical presentation of her breast cancer.

Methods

Study population

The study participants were patients at the Henry Ford Health System, the largest health care provider in southeastern Michigan. About 60% of the patient population at the Henry Ford Health System are insured through the Health Alliance Plan, a large, not-for-profit, mixed-model health maintenance organization. The remaining 40% have coverage through the traditional fee-for-service insurance, Medicare, or Medicaid.

We identified women diagnosed with primary breast cancers from the tumor registry of the Henry Ford Health System. The other eligibility criteria were: (i) date of diagnosis of the first primary breast cancer between 1 January 1999 and 31 December 2000; (ii) patients received treatment and post-treatment follow-up at either the main hospital campus of the Henry Ford Health System or one of its satellite hospitals or clinics, and (iii) pathological diagnosis of stage I, II, III, or IV. Women diagnosed with stage 0 breast cancer were excluded from the study since HER-2/*neu* testing does not influence clinical decisions about their course of treatment. Women diagnosed with recurrent breast cancer were excluded to reduce the potential confounding effect of disease severity.

Data collection

When a patient is first seen at any of the Henry Ford Health System facilities for any reason, he/she is assigned a permanent and unique lifetime medical record number and entered into the Master Patient Index, which serves as the central data repository for each patient. The Master Patient Index database is useful in obtaining demographic and health insurance data. The electronic medical records contain notes from physicians, radiology and pathology records, and clinical laboratory results.

The data collection of this project was exempt from requiring written informed consent, stipulated by the US Department of Health and Human Services regulation 45 CFR 46, Nos. 3 and 5. Data were collected from existing databases and no study participant was contacted. The Institutional Review Board at Henry Ford Health System approved this study (IRB # 1369).

We abstracted data on (i) patient characteristics, (ii) tumor characteristics, and (iii) results of HER-2/*neu* testing, date of request and specialty of physician who had submitted the request. Insurance plans were then categorized into fee-for-service, capitated insurance, Medicare, or Medicaid. If patients with Medicare Part A had supplemental policies, then their insurance was classified as fee-for-service or capitated, depending on its type. Patients with fee-for-service insurance were self-referred, whereas patients with capitated insurance were referred by a primary care physician to a surgeon or medical oncologist.

Statistical methods

We used descriptive statistics to summarize the characteristics of the study population. The variable 'age at the time of diagnosis' was categorized into six age groups: <40, 40–49, 50–59, 60–69, 70–79, and 80 years and older. We classified breast cancers based on their expression of the estrogen receptor status into two phenotypes: positive and negative. Cancer stage was classified as I–IV and nuclear grades as 1–3. Axillary nodal involvement was classified into four groups: (i) lymph nodes were not evaluated, (ii) evaluated but negative for metastasis, (iii) only sentinel node positive for metastasis, and (iv) sentinel and axillary lymph nodes positive for metastasis. Finally, we dichotomized the study participants into two groups 'evaluated for HER-2/*neu*' and 'not evaluated for HER-2/*neu*'.

We applied multivariate logistic regression to determine the variables associated with inclusion of HER-2/*neu* testing in the diagnostic workup of patients. In developing the best fitted model, we first estimated the individual effect of each variable on HER-2/*neu* testing. Correlations between different variables were estimated and the multi-collinearity effect was prevented by including in the model only variables with coefficient values of ≤0.70 [12]. Variables with a *P*-value of <0.10 from the univariate analyses were considered candidate variables. Interactions between variables were also tested at $P \leq 0.1$. The initial model was built using the forward selection approach. The final model contained only variables that were significant at $P \leq 0.05$ and interaction terms that remained significant at $P \leq 0.10$. We adjusted the final model for the year of diagnosis to account for time effects. Finally, we used the combination of logistic regression and the receiver operating characteristic (ROC) curve to detect the best discriminative factors for inclusion of HER-2/*neu* testing at the time of diagnosis [13,14]. The curve is a graphic display of predictive accuracy of the logistic model with the area under the curve equal to the C-index. A C-index of 0.8 or greater suggests that the model has some utility in predicting outcomes in clinical settings [15]. The Statistical Analysis System (SAS, Cary, NC, USA), version 8.2 was used to conduct the statistical analyses.

Results

We identified a total of 482 women from the tumor registry at Henry Ford Health System. After reviewing medical records, we excluded 31 women from the study because: (i) of electronic restriction on accessing medical records ($n = 16$, 3%), (ii) of recurrent cancers ($n = 2$, 0.4%), (iii) date of diagnosis was prior to 1999 ($n = 1$, 0.1%), (iv) patients were metastatic at the time of diagnosis and refused any medical intervention ($n = 4$, 0.8%), (v) patients opted to be treated elsewhere ($n = 4$, 0.8%), and (vi) referral to Henry Ford Health System for a second opinion ($n = 4$, 0.8%). A total of 451 women remained in the study.

The proportion of women whose cancers were evaluated for HER-2/*neu* was 51.9% ($n = 234$). Of these women, 72 (30.8%) were evaluated for HER-2/*neu* in 1999 and 162 (69.2%) in 2000, an ~2-fold increase (Table 1). On average women who were tested for HER-2/*neu* were younger (57.8 ± 13.4 years)

Table 1 Comparison of the two groups of women 'evaluated for HER-2/*neu* status' and 'not evaluated for HER-2/*neu* status' for selected characteristics

Variables	Tested for HER-2, *n* (%)	Not tested for HER-2, *n* (%)	*P*-value
Year of diagnosis			
1999	72 (30.9)	163 (74.8)	<0.0001
2000	161 (74.5)	55 (25.2)	
Age at diagnosis			
Mean (±SD)	57.8 (±13.4)	62.0 (±14.1)	0.001
Physicians' specialty			
Surgery	220 (95.2)	173 (79.4)	<0.0001
Oncologist	11 (4.8)	45 (20.6)	
Insurance type			
Capitated coverage	141 (60.3)	99 (45.6)	0.02
Fee-for-service	93 (39.7)	118 (54.4)	
Estrogen receptor status			
Positive	163 (69.7)	175 (80.6)	0.03
Negative	69 (29.5)	41 (18.9)	
Unknown	2 (1.3)	1 (0.5)	
Stage			0.66
I	119 (51.1)	102 (46.8)	
II	93 (39.9)	95 (43.6)	
III & IV	21 (9.0)	21 (9.6)	
Nuclear grade[2]			
Well differentiated	36 (15.4)	42 (19.4)	0.008
Moderately differentiated	89 (38.0)	104 (47.9)	
Poorly differentiated	106 (45.3)	65 (29.9)	
Unknown	3 (1.3)	6 (2.8)	
Nodal involvement			
Evaluated, negative	142 (60.7)	124 (57.1)	0.70
Positive, sentinel node only	32 (14.8)	34 (14.5)	
Positive, sentinel & axillary	37 (17.0)	48 (20.5)	
Not evaluated	10 (4.3)	24 (11.1)	

than those who were not (62.0 ± 14.1 years) (P = 0.001). Oncologists and surgeons requested testing of HER-2/*neu* for 11 (4.8%) and 220 (95.2%) patients, respectively. About 60% (n = 141) of women with capitated insurance coverage and 40% (n = 93) of women with fee-for-service insurance were tested for HER-2/*neu*.

Among women tested for HER-2/*neu*, 30% (n = 69) were estrogen receptor negative. Of women who were not tested for HER-2/*neu*, 19% (n = 41) were diagnosed with cancers not expressing estrogen receptors (P = 0.03). Finally, of the women who were tested for HER-2/*neu*, 45% (n = 106) were diagnosed with poorly differentiated nuclear grade cancers, compared with 30% (n = 65) women. This difference was statistically significant (P = 0.008).

Multivariate logistic regression modeling

Results from the multivariate logistic regression modeling are presented in Table 2. Type of health insurance, estrogen receptor status, and specialty of physician in charge of the patient's treatment were the best indicators for HER-2/*neu* testing. Women who were insured through a fee-for-service type insurance were less likely to be tested for HER-2/*neu* relative to those who were insured through a capitated insurance (OR = 0.55, 95% CI 0.36–0.85, P = 0.008). The likelihood of HER-2/*neu* testing increased by almost 2-fold if a woman was diagnosed with estrogen-receptor-negative cancer (OR = 1.92, 95% CI 1.15–3.21, P = 0.013). Finally, the likelihood of a woman being evaluated for HER-2/*neu* increased by almost 6-fold (OR = 6.2, 95% CI 2.88–13.33, P = 0.0001) if the referral physician was specialized in surgery. Results of the ROC analysis yielded C-indexes of 0.799, indicating a moderate discriminative model.

Discussion

We conducted a retrospective analysis to assess the proportion of women who were tested for HER-2/*neu* shortly after the availability of standardized laboratory kits for use in the clinical

Table 2 Variables best associated with HER-2/*neu* testing of breast cancer patients at the initial clinical presentation of cancer: results of the multivariate logistic regression analyses

Variable Model (goodness of fit = 0.342)[3]	Tested for HER-2	Not tested for HER-2	OR[1]	95% CI[2]	*P*
Insurance type					
Capitated coverage	141	99	1.00	–	–
Fee-for-service	93	118	0.63	0.41–0.94	0.027
Estrogen receptor status[4]					
Positive	163	175	1.00	–	–
Negative	69	41	1.96	1.15–3.21	0.013
Physician's specialty					
Oncology	11	45	1.00	–	–
Surgery	220	173	6.21	2.88–13.33	0.0001

[1]Odds ratio.
[2]95% confidence interval.
[3]Adjusted for the year of diagnosis.

setting. During the period of 1999 and 2000, testing for HER-2/*neu* status was based on the discernment of the physician in charge of the patient's treatment; thus, we evaluated the variables that best discriminated for inclusion of the test in the diagnostic workup of breast cancer patients. Women whose cancers were characterized by the absence of estrogen receptor were more likely to be tested. Our finding concurs with the clinical correlative studies and laboratory experimental studies describing an inverse association between the HER-2/*neu* biomarkers and the presence of estrogen receptors [2–4,16].

We report that the differential in testing of the HER-2/*neu* biomarker could have been in response to the physicians' learning process, the associated diagnostic costs, and patients' health insurance coverage. Between 1999 and 2000, the proportion of women who were tested for HER-2/*neu* increased by almost 2-fold. We attribute this increase to the learning curve phenomenon. Our literature search of the Medline database yielded a >1.5-fold increase in the scientific coverage of HER-2/*neu* laboratory testing between 1999 and 2000. This increase might have been an influencing factor for accepting the validity and reliability of the kits for diagnostic purposes. Also, in 2000, a series of recommendations regarding HER-2/*neu* testing, one of which was that the routine testing of HER-2/*neu* should be a component of the diagnostic workup for every woman diagnosed with breast cancer, was published [10,11]. Finally, patients' knowledge about HER-2/*neu* testing might have been another reason for the observed increase. Within this study population, two women were evaluated for HER-2/*neu* despite having excellent prognoses (well differentiated tumor grade, stage I, no nodal involvement and positivity for hormonal receptors). An in-depth review of their medical records indicated that these patients were self-educated about the issue of HER-2/*neu* testing and had requested that their cancers be tested for HER-2/*neu*.

Surgeons were more likely to test their patients for HER-2/*neu*. We attribute this observation to the group of surgeons with a subspecialty of surgical oncology. There is no support in the literature for the effect of surgical specialty or clinical experience on HER-2/*neu* testing or other biomarkers with potential diagnostic value. However, others have reported improved survival of breast cancer patients when treated by surgical oncologists [17]. The effect of surgeon specialization on increased survival among breast cancer patients has been attributed to: (i) pure volume effect, (ii) surgical skills and (iii) more appropriate use of adjuvant therapies [17]. In this study, the observed higher percentage of requests for HER-2/*neu* testing by surgical oncologists might have been due to the 'volume effect'. At the Henry Ford Health System, the majority of breast cancer patients are referred to surgical oncologists for confirmation of a suspicious mammogram or a palpable lump in the breast.

Women who were insured through a fee-for-service plan were less likely to be tested for HER-2/*neu* relative to those who had coverage through capitated insurance. There is no controversy regarding billing for HER-2/*neu* testing, however, reimbursement may vary by payer and by national region [18]. Participants in this study were from the same area; therefore, reimbursement variation by region could not have been an influencing factor. Also, since the participating physicians at Henry Ford Health System provide medical care to patients regardless of their insurance plan (fee-for-service, capitated, Medicare, or Medicaid), the variable 'physician in charge' was not a significant confounding factor. Our data indicate that insurance and the out-of-pocket costs might have been the reasons for the observed differences in HER-2/*neu* testing. Evaluation of the billing data and consultation with several individuals in the Department of Patient Financial Services and the Revenue Manager at the Department of Pathology suggested that between 1999 and 2000 the largest fee-for-service health insurance provider for this population accepted a maximum of $675.35 and $181.90 for HER-2/*neu* testing, depending on the type of laboratory testing. In contrast, capitated insurance covered the entire cost. Therefore, we propose that some physicians might have refrained from HER-2/*neu* testing simply to reduce the burden of out-of-pocket cost on

their patients. The disparity in the health service delivery and utilization of effective care between fee-for-service and capitated insurance has been reported [19–21]. One of the theoretical benefits of capitated insurance is the philosophy of reducing cost by emphasizing primary and secondary interventions and transferring the cost-saving initiatives to patients. However, others suggest that health care providers tend to increase utilization of services for patients whose insurance coverage has minimal or no out-of-pocket costs in order to recover the revenue losses caused by cost-sharing insurances [22]. The observed higher probability of HER-2/*neu* testing in the diagnostic workup of breast cancer patients with capitated insurance might have been to offset losses in revenue. Regardless of the reason, disparity in quality of care delivery due to the effect of health insurance exists and has been reported for medical conditions other than breast cancer [23]. In 2001, many institutions including the Henry Ford Health System implemented policies that testing for HER-2/*neu* should be a component of the diagnostic workup of any woman newly diagnosed with invasive breast cancer of any stage. Implementation of this policy has standardized the quality of care for every single breast cancer patient.

We acknowledge the limitations of the present study. Firstly, the scope of this study was limited to only one institution and one geographical region. Secondly, due to the relatively small sample size the study did not have adequate statistical power to discern the influence of socio-economic status on HER-2/*neu* testing.

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